

Practical Approach to Treatment of Sjögren's Syndrome – Dry Mouth and Gynecologic Complaints

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Abstract

Sjogren's syndrome (SS) is characterized by dry eyes and dry mouth, but there is a wide spectrum of additional symptoms due to dryness. The treatment of dry mouth remains largely unsatisfactory and the correlation of dry mouth symptoms with either minor salivary biopsies or salivary gland flow rates remains low. These currently used methods of diagnosis (and therapeutic outcome) measure predominantly the transport of water and the transporters (acini and ducts) of water, electrolytes and selective associated proteins. Proteomics of saliva in SS patients have demonstrated the altered content of salivary proteins and their post-translational processing in comparison to age matched individuals. Also, the microfloral colonization of the mouth and the content of the "biofilm" differ in SS patients. However, it is likely that the major factor that remains unknown in the SS patient's symptoms of dryness reflect the poorly understood role of oral mucins that play a key role in the viscosity of movement of the tongue and oral membranes. Saliva is a water/mucin mixture that contributes to the comfort of the oral mucosa during chewing, talking and swallowing. Also of great importance, the symptoms of "burning mouth" are frequently exacerbated by low-grade oral erythematous yeast infection, especially as a complication of dentures that are frequent in this population of patients. Another important factor is local neuropathy of the oral surfaces or the "burning mouth syndrome". All of these "dry mouth" symptoms are exacerbated by "chronic central sensitization," the current term for fibromyalgia, where afferent pain stimuli are amplified at the level of dorsal column or centrally in the brain. These latter symptoms are exacerbated by stress and sleep disturbances that reflect the complex immune-neuro-endocrine-exocrine axes. Also, a wide variety of medications used for neuropathy or fibromyalgia, as well as other medical problems in these patients, may exacerbate the oral dryness symptoms. Similar considerations apply to

gynecologic complaints and may greatly affect the patient's quality of life, although rheumatologists and internists rarely ask about gynecologic or urologic symptoms or provide guidelines for their treatment. In view of the limited time available for patient visits, we believe patient instruction by e-mailing guidelines to the patient may provide a method to provide patient education and help guide physician's approach to treatment.

INTRODUCTION —

SS is characterized by dryness of the eyes and mouth, due to lymphocytic infiltrates of the lacrimal and salivary glands. The current clinical and laboratory criteria for diagnosis of primary Sjogren's syndrome (SS) are presented in Table 1. SS is predominantly a disease of women (female: male ratio of 9:1) with onset at two peaks—during the age 20 to 30 yrs and a second peak in the mid 50's. One of the key problems that face the busy clinician is simply the diagnosis of SS, as compared to either systemic lupus erythematosus (SLE) or scleroderma (PSS). Indeed, these disorders frequently overlap and a subset of SLE and PSS patients have dryness that is termed secondary SS. In order to easily allow primary care physicians and patients to review the criteria, we have included Tables 1 (Criteria for SS), Table 2 (Criteria for SLE), Table 3 (Criteria for Scleroderma) and Table 4 (Criteria for Fibromyalgia). The recently described guidelines for Organ Damage Index (Table 5) and Disease Activity Index (Table 6) are also presented as a reference for the busy clinician.

Both genetic and environmental agents are involved in pathogenesis of SS. The genetic factors include transplantation antigen related loci such as HLA-DR3 and related genes modulating cytokines such as type I interferon, tumor necrosis factor and interferon gamma. These genes play a role in determining autoantibody production. The patients have a characteristic autoantibody profile including a positive anti-nuclear antibody (ANA) and antibodies against nuclear proteins Sjogren's associated A antigen (60 and 52 kd) and B antigen (45 kd). However, patients may also present with anti-centromere antibodies or ANCA while still exhibiting features of primary SS and the type of autoantibody is most clearly correlated with the HLA-DR phenotype (1-3).

Environmental factors also play a role but no agent has been shown to be necessary and sufficient. The most commonly proposed agents have been Epstein Barr virus, other herpes virus family members (HHV-6), endogenous retrovirus, and coxsackie virus. Also in animal models, exposure of animals to a dry wind tunnel induces SS like lacrimal gland lymphocytes that can be adoptively transferred to naïve mice.

There is an overlap between SS and a subset of SLE patients, as manifest by shared genetic factors, antibodies, and clinical features. However, it is easiest to think of SLE as a disease derived from antibody and immune complex mediated

end organ damage, while SS patients have a more lymphocytic aggressive disorder. Indeed, the infiltration of the characteristic lacrimal and salivary glands (that normally lack lymphocytes as extra-nodal sites) indicates the ability of SS lymphocytes to enter other tissues such as lung, nerve, and increased rates of lymphoma. The current criteria for SLE and for scleroderma (progressive systemic sclerosis, pSS, which is another condition that may overlap with SS) is presented in Table 2. When patients fulfill criteria for both SS and another well recognized autoimmune disorder such as rheumatoid arthritis (RA), SLE, or pSS—the patient is labeled as SS secondary to the other disorder in order to bring the physician’s attention to the particular complications and therapies of both conditions. However, the approach to dry eyes and dry mouth in patients with primary and secondary SS is similar.

Sjögren's syndrome (SS) is a multi-system disorder that may present to many different specialists including general internal medicine and its subspecialties (especially rheumatology, chest medicine, neurology, hematology, nephrology, psychiatry), surgery and its subspecialties (especially ophthalmology, otolaryngology), and related specialties such as oral medicine. Medications used for certain manifestations, such as tricyclic agents for neuropathy or fibromyalgia may greatly exacerbate the symptoms of dryness. Similarly, agents used for blood pressure, cardiac arrhythmia and many other medications possess significant anti-cholinergic side effects. An important role of the primary physician is to recognize the role of medications in exacerbating dryness conditions and to choose alternative medications when possible. This paper will focus on a practical approach to therapy of dryness of mucosal surfaces.

I. General Principles of Dry Mouth Treatment

Recognition of certain environments that exacerbate dry mouth

Patients should employ methods to prevent oral complications. It may take two or three days to build (heal) the oral mucosal film, but only two to three hours in a dry environment for it to be disturbed. Among considerations to counsel patients:

- a) Travel to areas with low humidity and dry winds are obvious red flags. The use of water in aerosol sprays, as well as nasal humidification are encouraged. It is best to use these in a preventative manner, rather than playing “catch up” after symptoms have developed.
- b) Automobile travel not only involves dry heating and air conditioning, but also presents additional problems of pollution from the road. The avoidance of dust or use of masks (when necessary) will help minimize the impact.

- c) Many large offices that use central heating/air conditioning are extremely dry. Patients need to optimize their work environment by having watered plants or small humidifiers, as well as air filters if the pollution/dust level is high.
- d) Recognition of medications with anti-cholinergic side effects, including over the counter sleeping aids and cold medications that frequently contain potent drying agents.
- e) Nasal congestion that leads to increased mouth breathing, particularly at night
- f) Recognition that there is a normal diurnal variation in saliva (as well as tear) flow, with the rates of basal flow being lowest at night. Therefore, any medication with anticholinergic side effects which must be taken is preferably not given at night
- g) Recognition that a dry mouth is not necessarily a painful mouth. The onset of increased after oral antibiotics is a strong suggestion that the SS patient, particularly if using corticosteroids, has a low grade yeast infection of the mouth.

The increased frequency of use of artificial saliva and lubricants by patients in these environments may help to prevent complications and increase comfort. We also provide Table 7 as a guide for prevention of Dental Caries, as well as Tables 8 and 9 for treatment of oral yeast.

We advise our SS patients to anticipate:

- ▶ *dry outdoor environments,*
- ▶ *dry indoor environments,*
- ▶ *increased pollution (including presence of smokers),*
- ▶ *strong winds,*
- ▶ *increased time in areas that are stressful, since literature is full of statements that the "heroine's heart beat fast and her mouth was dry" in anticipation of.....*

Thus...as an individual "weather forecast" allows you to choose your clothing, your identification of your "environmental stress" will allow the patient to plan for their oral surface health, and prepare to "dress" their mouth accordingly.

As referenced above, another important environment to expect -- and prevent -- SS dry eye complications including corneal abrasions is the Operating Room where the humidity is very low, and particularly in the post-operative recovery room where the patient frequently has non-humidified oxygen administered by a facemask. To that end, Table 10 summarizes precautions at the time of surgery:

- a) We recommend that patients use an ocular and oral lubricant prior to surgery to help prevent complications.

- b) As many operating rooms do not have certain specialized medicines used to treat the eyes of the SS patient available, we urge patients to *take their eye/mouth medications with them to the hospital* (despite the hospital's instructions to leave medications at home), as these "specialty" items are not on most hospital formularies.
- We remind patients to ensure that their attending surgeon/hospitalist writes an order in the hospital chart permitting the patient to bring their own SS medicines from home and self-administer PRN and/or have them administered in the hospital.
- c) We advise the use of artificial tears be started prophylactically in most patients before they go into dry environments.

II. XEROSTOMIA- TOPICAL TREATMENT AND ORAL AGENTS TO STIMULATE SECRETION

A. Treatment of dry mouth —

Treatment of dry mouth claims to alleviate symptoms and prevent complications such as dental caries, gum disease, halitosis, salivary gland calculi, and dysphagia. Two major components of this regimen are stimulation of existing salivary flow and replacement of salivary secretions.

Saliva has multiple functions within the oral cavity that include:

- 1) *Lubrication of the mucosa* so that the tongue can help with cleaning out residual food that leads to dental plaque and bacteria;
- 2) *Buffering of acids* that reabsorb calcium from teeth;
- 3) *The ability to modulate viral, bacterial, and fungal populations* in the mouth.

C. Replacement of oral secretions —

Replacement of oral secretions is most simply accomplished by frequent sips of water. The water does not have to be swallowed, but can be rinsed around the mouth and expectorated. Although water provides temporary moisture, it does provide the lubricating properties that are characterized by the mucin/water mixtures that constitute normal saliva.

A number of artificial saliva preparations that provide more viscosity/lubrication than water are available. These preparations contain hypro-mellose or methylcellulose, sometimes with animal mucins to reduce viscosity.

There seems to be wide variation in individual preferences and, given the large number of products available, it is logical to encourage patients to try several different formulations. One explanation for the variable response may be differences in viscosity (4).

Artificial salivas provide longer lasting lubrication than water and are therefore useful at night or in patients with dentures. Most are dispensed as sprays, but lozenges or pastilles are available to subjects for whom sprays would be difficult to use, due to arthritis.

If simple measures such as sips of water or sugar-free chewing gum are insufficient, it is reasonable to try a spray such as *Oasis*®, *Salivart*®, *Mouth Kote*® and several other brands have recently appeared. In other patients, a gel such as *Oral Balance*® can be helpful particularly at night.

D. Stimulation of existing salivary flow —

- Simply sucking on sugarless candies or dried fruit slices such as peaches or nectarines can stimulate flow in many patients.
- Citrus flavored sugarless tablets (e.g., *Salivasure*®, Scandinavian Health and Beauty Products, Perkasi, PA) are available. These tablets may also contain malic acid, normally found in fruits such as apples or pears, which stimulates salivary flow.
- Use of maltose lozenges may reduce symptoms of oral dryness as suggested by an observational study in 100 subjects (5).
- Sugar-free chewing gums, containing various sweeteners such as aspartame, saccharin, and sorbitol can also be helpful.

Care must always be taken not to increase the risk of dental caries.

E. Oral agents that stimulate saliva

Secretagogues (Table 13) —

Two muscarinic agonists (*pilocarpine* and *cevimeline*) have recently been approved as secretagogues for the treatment of symptoms of xerostomia in Sjögren's syndrome (SS) [54]. These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function.

Cevimeline —

Cevimeline (Evxac®) is a derivative of acetylcholine with a higher affinity for muscarinic M1 and M3 receptors on the lacrimal and salivary epithelium than for receptors on heart tissue (6). It is also known in the literature as (±)-cis-2-Methylspiro[1, 3-oxathiolane-5, 3'-quinuclidine, SN-201 and AF106(7). It has been shown to significantly increase saliva flow and patient oral "quality of life" in two double blind US studies(8, 9). Doses of 30 or 60 mg three times daily alleviate the symptoms of dry mouth, dry eyes, and stimulate salivary flow; the 30 mg dose is nearly as effective as the higher dose and is better tolerated (10).

The efficacy of cevimeline was illustrated in a study that randomly assigned 197 patients with either primary or secondary SS to cevimeline or placebo (11). Patients' global assessments of dryness were improved significantly more often by cevimeline 30 mg three times daily than by thrice daily doses of 15 mg or placebo (65, 32, and 35 percent, respectively). It has also been reported in double blind studies in other countries including Japan(12, 13) and China(14).

Major side effects of cevimeline include excessive sweating, nausea, rhinitis, diarrhea, and visual disturbances. It is contraindicated in patients with intractable asthma, narrow-angle glaucoma, and active iritis, as these patients were excluded from the clinical trials.

Cevimeline (also known in neuropharmacology literature as AF102) was originally developed for treatment of Alzheimer's disease (where M1 agonist activity is neuroprotective) and found to increase salivation through its M1 and M3 agonist activities (5)[55]. It was subsequently shown effective in increasing saliva flow and symptom improvement in SS (5).

In addition to simply increasing saliva flow, Cevimeline induced changes in the protein content of saliva, including the release of aquaporin 5 (AQP5) with lipid rafts, amylase, mucin, and lysozyme(13, 15). Changes in saliva AQP5 levels after cevimeline administration occurred simultaneously with changes in saliva flow rates. Aquaporins selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes.

Also known as **water channels**, aquaporins are integral membrane pore proteins and AQP5 has been implicated in both salivary/lacrimal glands(16-19) and in brain(20, 21) as an important regulator of water transport after cholinergic stimulation.

Pilocarpine —

(Salagen®), a muscarinic agonist that stimulates predominantly muscarinic M3 receptors used at doses of 5 mg three or four times daily, can significantly increase aqueous secretions in patients with residual salivary gland function (22, 23)[. Unfortunately, side effects (sweating, abdominal pain, flushing, increased urination) may limit its use. Pilocarpine was initially used for treatment of radiation xerostomia and subsequently for SS (5, 24).

The longest reported study of pilocarpine in SS evaluated 20 patients taking 10 to 30 mg/day for one year.

- Six patients complained of sweating and four of abdominal cramps (22). None of the patients chose to discontinue taking pilocarpine because of these side effects.
- The subjective benefit in oral comfort did not correlate closely with objective changes in salivary flow, indicating the importance of mucin in

forming a water/mucin gel that lowers friction associated with movement of the buccal mucosal surfaces and the tongue.

In addition to effects upon xerostomia, pilocarpine may improve symptoms of ocular dryness, although without any objective change in tear production (25).

In our experience, *pilocarpine* has a shorter onset of action but also a shorter duration of action with suggesting dosing four times a day. This leads to a narrow window between efficacy and side effects of sweating. Several reports have suggested benefit from time release preparations of pilocarpine as buccal inserts(26, 27) or as transdermal application(28).

Cevimeline is generally used three times a day. However, we recommend gradually increasing the dose and taking it about 30 minutes before meals. Initially, patients may have some increased symptoms of gastric acidity (also stimulated by the muscarinic receptors), but this can be minimized by use of a proton pump inhibitor while initiating therapy.

Pilocarpine and cevimeline (both muscarinic agonists) do more than increase the flow of water. Studies of saliva from treated patients show changes in the types of small molecules termed defensins and alterations in post-translational modification (particularly glycosylation) in saliva (29, 30).

Numoisyn—

Numoisyn is a newly available product that appears to be the same as Salinum(31), a linseed oil extract that is available as a liquid and as a throat lozenge. It has been reported in patients with oral dryness related to radiation but no data has been published on SS patients as determined by PubMed search.

Oral interferon alpha-- was reported as promising in early studies (32) [10,11]. However in the pivotal trial (33), the salivary flow rates in the interferon-treated group and the placebo group were not statistically significant. Neither were there significant differences in the changes in self-reported oral comfort or symptoms of oral dryness, throat dryness, or difficulty swallowing dry food.

F. Oral hygiene

It is extremely important that the SS patient regularly:

1. floss their teeth after meals,
2. receive regular professional dental hygiene treatments including fluoride treatments (discussed below) at frequent intervals such as every three months [33], and recognition that certain fluoride treatments might discolor dental enamel or denture material.
3. recognize the role of dietary factors with respect to the correlation between sucrose intake and caries [34].

4. *maintain the use of particular uniquely beneficial toothpastes.* Most commercial toothpastes have the detergent sodium lauryl sulfate (SLS) which may be irritating. Thus, other toothpastes are available that use other detergents such as: Biotene®, Tom's of Maine®, and Spry Toothpaste® with xylitol (many products are listed on the website www.dentist.net with selection of the dry mouth section of products.

Although frequently grouped together, it is important to consider dental caries as distinct from periodontal disease.

Development of dental caries is a major problem in subjects with dry mouth. Avoidance of this complication in subjects with SS follows the same principles as in the rest of the population and these include:

1. *meticulous oral hygiene* with frequent flossing,
2. *frequent visits to the dentist* (at least every six months), and
3. *plaque control.*

A common problem is that cosmetic dentists may place "full veneer" crowns over small carious regions resulting in these areas are no longer being accessible to intensive dental care. As a result, the carious tooth may progress until the tooth is lost and crowns fail.

Again, toothpastes specifically designed for dry mouth are available (e.g., Biotene® toothpaste, Laclede Labs, Gardena, CA). These lack the detergents present in many toothpastes that can irritate the dry mouth.

Additional recommendations:

- a) *Toothbrushes with special features* include interdental brushes (for cleaning between teeth)
- b) *electric toothbrushes* (for patients, such as those with arthritis, who are unable to use a normal brush effectively).
- c) *Use of dental floss*
- d) *fluoride* either as toothpaste or mouth rinses and *fluoride varnishes* [14].

Oral candidiasis —

A dry mouth is not necessarily a painful mouth, but may become a painful mouth if the patient develops oral candidiasis, and patients with SS are at greater risk of developing this complication (34). Thus, patients can have dry mouth for many years and only present to the clinician when the mouth becomes painful. Also, there may be a change in the sense of taste and examination reveals a decrease in the number of papillae on the tongue.

Oral candidiasis is particularly frequent following antibiotic treatment or the use of glucocorticoids. Affected patients present with mouth pain, erythematous or white patches on the mucosal surfaces, and loss of tongue papillae. A common clue to

the presence of oral candida is angular cheilitis and atrophic changes of the buccal mucosa(35).

The appearance of erythematous candidiasis (one of the most common presentations) on the roof of the mouth is small red petechial lesions(36). This appearance is different than the plaque like candida infection that clinicians are used to looking for in patients with severe immunosuppression.

Another presentation of low grade candidiasis in the SS patient is leukoplakia-like lesions, especially in the buccal recesses. The candida infection can occur despite a careful program of regular dental hygiene(37) Treatment of this low grade erythematous candida is a slow process that involves:

- a) treatment of the angular cheilitis with topical chlortrimazole cream twice a day for at least 2 weeks;
- b) special cleaning treatment of the dentures (if being used by patient) at night by cleaning in solutions that will disinfect the denture without discoloring the materials (0.2% chlorhexidine solution is often used) and additionally using nystatin powder to “brush” the dentures after they have soaked overnight in the cleaning solution.
- c) use of oral mouth rinses 3 to 4 times per day with a solution that contains “Mylanta” as the vehicle (since most other oral rinses contain alcohol based dilutents; 300 ml of Mylanta can be added to nystatin elixir solution (20ml), benadryl liquid (20 ml, to serve to decrease pain) and doxycycline 100 mg. (In the past, we have suggested “peptobismal” as the vehicle, but the formulation of this compound has recently been changed, so now we recommend “Mylanta” as the vehicle.) This mouth rinse is available in many pharmacies where it is known as “Stanford Radiation Therapy Mouth Rinse®” or as “XYZ Mouth Rinse®” as patients use it with severe oral dryness after radiation to head and neck. In our clinic, we have the pharmacy simply dispense the components, as this is much less expensive than having the pharmacy “compound” the mixture.
- d) nystatin 200 mg tablets (1 per day) for 5 days; in some patients, the yeast may be resistant to nystatin or chlortrimazole and topical amphotericin may be required(38).
- e) nystatin vaginal suppositories (sucked like lozenges) or amphotericin B lozenges used daily; they are taken with sips of water for periods and used once or twice a day for up to 6 weeks (34).

Prevention of dental caries —

The loss of teeth in SS patients results from a combination of low oral pH that facilitates loss of dental calcium and the alterations of oral flora that lead to accelerated decay (13, 39) (40, 41). These problems have been recently reviewed (42). (43).

For individuals with very low to no salivary production, the amount of phosphate and calcium ions available for incorporation onto the tooth surface and enhancement of the remineralization process may be limited. These individuals could possibly benefit from the exogenous addition of calcium phosphate ions commercially available as toothpaste, in specialized chewing gums, and as a solution.

A double-blind clinical trial examined the efficacy of a dentifrice containing calcium phosphate and found modest benefit in the prevention of root caries in SS, but no benefit on coronal caries was noted (43). These findings are consistent with the observation that individuals with salivary dysfunction are prone to root and incisal caries, rather than coronal caries.

Caphosol® is one of the more common prescription preparations that is a supersaturated calcium phosphate rinse.

Another clinical trial examined the caries preventive effect of a mouth rinse containing casein derivatives coupled to calcium phosphate in patients with Sjögren's syndrome and dry mouth secondary to radiation therapy [42]. The mouthwash failed to show complete efficacy (43). The majority of studies supporting the addition of calcium and phosphate as an aid to remineralization have been primarily short-term studies in animals and humans. There is currently no agreed-upon formulation/concentration of calcium phosphate or consensus on how often exposure should occur which could influence the results of any clinical trial. Definitive proof would require large long-term clinical trials, which are notoriously difficult and expensive (44).

Artificial sweeteners that are not fermentable by acid-producing bacteria have also been suggested to aid remineralization process (45). Initial data primarily from studies done with children has shown that certain natural sweeteners such as xylitol and sorbitol (usually in a chewing gum formulation) have a significant anti-caries effect. There has been some suggestion that the caries-preventative effect of xylitol/sorbitol is due to the effect of chewing alone, via the production of saliva (42, 43). But other mechanisms have been suggested including:

- a) the growth inhibition of caries-inducing bacteria,
- b) the selection of xylitol-resistant strains with a resultant shift to less virulent and cariogenic strains, and

the binding of xylitol to surface receptors on *Strep. mutans* species modulating their function (46).

The mainstay in the prevention of dental caries remains fluoride (47). A high dose 5 percent sodium fluoride varnish is currently available in the United States, but apparently not as widely used in the United States as in Europe where it was developed and tested primarily in children. The prevention of caries in SS patients is summarized in Table 5.

Topical fluoride

Two mechanisms by which **topical fluoride** promotes remineralization include:

- 1) the development of a crystalline protective veneer at the site of demineralization; and,
- 2) inhibition of bacterial metabolism, and thus reduction of their acid production.

The theoretical advantage of using the varnish is not only in the higher level of fluoride, but also in the sustained release delivery system.

One *in-vitro* study determined that a single application of the varnish could release fluoride for up to six months (43). Varnish application is fast and easy and does not necessarily require professional prophylaxis prior to application, and can be applied directly to the root and incisal surfaces that are most vulnerable to decay in the SS patient population (48).

Chlorhexidine (CHX) is a topical antimicrobial agent that is used to decrease the intra-oral bacterial load thought to contribute to periodontal disease and caries (49). In addition, CHX has an antifungal effect that is relevant to the SS population. In our experience, the available CHX oral rinses have not been well tolerated by the SS patient group. Chlorhexidine is now being developed in the varnish format and as a chlorhexidine-fluoride combination varnish that may be more acceptable to the SS population.

Dentures and Implants —

As teeth are lost, there is some concern as to whether patients with SS have more difficulty wearing dentures because of the decreased moisture in the mouth. No systematic clinical trials have addressed this question.

In general, dentures cannot replicate the efficiency and comfort of having your own teeth. There are scattered case reports regarding the ability of patients with SS to handle implants. The majority of reported cases where patients with SS received implants appears favorable, but does not provide long-term follow-up (41).

A rational approach to whether implants are feasible for a patient with SS should be determined on a case-by-case basis, which includes the possibility of the influence of a systemic disease. This topic is well discussed in an article on implants and the dry mouth patient by James Scuibba. <http://www.sjogrens.org/syndrome/reading.html>

Two new products to brighten teeth have been released and are available over-the-counter for home application (43). These whitening treatments are available at local shopping malls and “health fairs,” where they may be administered by individuals with little or no experience with SS patients. Both are fairly acidic at pH~5.0 and pH~4.5, respectively:

- One is a polyethylene strip containing peroxide;
- The other is a peroxide-containing gel.

In a data sheet provided by Colgate Pharmaceuticals, their product is “non-recommended” for “almost any medical condition” with dry mouth and advises that the individual consult their doctor/dentist prior to using. In the patient with the most severe salivary dysfunction, there would be a theoretical concern about an increased contact time of the product to the mucosa and to the tooth surface. With professionally applied whitening processes, these variables can be better controlled if required.

A remineralizing solution containing calcium phosphate and a fluoride treatment may be considered in conjunction with a bleaching treatment. Again, the use of a whitening agent should be decided on a case-by-case basis in consultation with a professional familiar with the products. It should be noted that the majority of studies on tooth whitening have focused on efficacy rather than safety.

Genetically engineered acid-free bacteria are being developed to compete with the intra-oral caries causing bacteria with the ultimate outcome of a population shift to a non-caries promoting bacterial population (50). A caries vaccine has been in development for several years but not yet approved for use (51). Clinical trials are also underway to test the oral topical application of an engineered tobacco plant secretory IgA specific to a surface protein and other recombinant products on strep mutans ability to adhere to dental enamel (46, 52).

In denture wearers, a form of *oral candidiasis*, characterized by petechial lesions on the palate, may be visible only after the removal of the dentures. Suggestions for treatment of oral candida are summarized in Tables 6 and 7.

III. Contributing Factors to Dry Mouth

Nasal dryness, sinus blockage by tenacious secretions and associated “mouth breathing” —

Nasal dryness should be considered in conjunction with xerostomia, since blocked nasal passages increase mouth breathing and exacerbate oral dryness. Saline nasal sprays are available and should be used frequently.

In many patients, the use of humidifiers followed by gentle nasal lavage to remove encrusted secretions may be helpful (Table 10). The paradoxical finding of rhinitis in a patient with SS may be due to vasomotor rhinitis and often will respond to nasal lavage followed by a topical inhaled nasal glucocorticoid

and/or albuterol. Also, humidification can be achieved using products such as *Ocean Spray*®. Additional causes of nasal blockage, including nasal polyps and sinus infection, should be sought and treated appropriately.

At our clinic, we have found that "**nasal lavage**" may prove helpful in treatment of dry nose as well as dry mouth (Table 10). The patients may irrigate their sinuses using a nasal syringe or use more automated methods of sinus lavage commercially available (www.hydromedonline.com). The general procedure is to first achieve humidification of the sinus (either a warm shower or use of a cool mist humidifier), followed by nasal lavage and then a topical corticosteroid spray.

Also of use are products for the dry nose such as Ayr Saline Nasal Gel®, Breathe Right Saline Nasal Spray®, Ocean Nasal Spray® (and the newly available Ocean Plus®), Pretz Spray®, and Xlear Nasal Wash with Xylitol®.

Laryngotracheal reflux —

It is common for SS patients to exhibit symptoms of recurrent sinusitis, or allergy such as "post-nasal" drip or frequent "throat clearing" with mucus [15]. Many patients with these complaints have acid reflux that results in laryngotracheal irritation, that stimulates vagal responses that mimic sinusitis. If reflux and laryngotracheal irritation are not suspected, and treatment with antibiotics is initiated for sinusitis, the result is likely to be oral candidiasis.

Treatment approaches for laryngotracheal irritation due to acid reflux include twice daily use of a proton pump inhibitor, three times daily use of liquid alginate (*Gaviscon*®), and avoidance of late night meals and caffeine. In some patients, promotility agents may be required and the assistance of an otolaryngologist with experience in distinguishing sinusitis and tracheal reflux is helpful in both diagnosis and therapy. (See "Medical management of gastroesophageal reflux disease in adults.")

Burning Mouth Syndrome and Fibromyalgia

In many patients, the symptoms of dryness or mouth pain are out of proportion to the objective findings on physical exam as well as salivary function scans. In some of these individuals, it has been proposed that they have a local neuropathic process termed "burning mouth syndrome." (Table 11)

In other patients, the patients may have amplification of symptoms due to "central sensitization," the current term used for description of fibromyalgia. In recent years, the distinction of this pain amplification has been distinguished from depression although the same types of medication used for depression or diabetic neuropathy have proven helpful. It is worth noting that the mainstay of neuropathy is tricyclic agents, which will exacerbate dryness due to their anticholinergic side effects (Table 12). The role of "fibromyalgia" in patient symptoms and physician global assessment should not be taken lightly as this

appears to be the dominant problem of patient's complaint and the reason that so many medications fail in clinical trial. Thus, "fibromyalgia" or "central sensitization" is the "elephant in the exam room." To signal our respect to this unknown creature that dominates our approach to therapy in SS, we have included Fig 1 showing the elephant in the room with her dry eyes/dry mouth as well as cognitive changes and myalgia.

IV. Gynecologic Complaints

. Gynecologic and Obstetric (Table 14)--

Vaginal dryness often leads to painful intercourse (dyspareunia) (53, 54). It is important to be reassured that this does not occur in all Sjögren's patients, even those with severe mouth and eye dryness (55, 56).

Many women with Sjögren's syndrome are interested in the risks of pregnancy and risks to the baby. Obstetrical authorities report slightly higher rates of recurrent fetal death and congenital heart block in those pregnancies complicated by maternal autoimmune disease (57).

In rare patients, fetal loss has been associated with presence of the antibodies called "antiphospholipid antibodies," "lupus anticoagulant," and anticardiolipin antibodies (58-60).

Congenital heart block is an abnormality of the rate or rhythm of the fetal or infant heart. Certain autoantibodies, such as an antibody called "anti-SS-A," have been associated with congenital heart block in the newborn. These

autoantibodies may be present in patients with systemic lupus erythematosus and with Sjögren's syndrome, as well as in patients with no apparent disease. Antibodies other than anti-SS-A have also been associated with neonatal heart block (58, 60, 61).

However, it is important to reassure patients planning families that the vast majority of patients with Sjögren's syndrome have babies with no congenital abnormalities. Thus, we encourage family planning to be conducted without this being a major consideration.

Nevertheless, it is important for patients anticipating pregnancy (or those with multiple prior miscarriages) to have screening blood tests and that their pregnancies are supervised by obstetricians experienced in handling patients with autoimmune diseases. If a pregnant patient requires corticosteroids for their medical condition, we suggest dexamethasone (decadron, rather than prednisone) since it crosses the placenta and will provide protection to the fetus (62).

Abnormal PAP smears have been reported at higher frequency in women with SLE (63) (64), and it is likely that similar findings will occur in SS patients. The elevated frequency of abnormal Pap smears were more common among SLE patients than controls, even after adjusting for HPV status. The use of

immunosuppressant agents was not associated with abnormal Pap smears. Thus, it appears that SLE-associated immunosuppression increases susceptibility to HPV infection (63). A potential link may be increased susceptibility to HPV infection in SLE (and SS) patients with a higher frequency of a particular allele in the TNF promoter.

A team approach combining both rheumatology and obstetrics can be used to optimize the outcome for both mother and baby.

In our experience, flares of Sjögren's have been common after delivery and we often recommend steroid coverage at the time of delivery and in the post-partum period in some patients.

Vaginal Dryness (Table 14) is a problem that is prevalent but not often discussed with the rheumatologist due to patient embarrassment. However, the patient should be encouraged to discuss with their gynecologist a variety of suitable lubricants are available:

- Astroglide®
- Estrace Vaginal Cream®
- Feminaease®
- Lubrin Vaginal Inserts®
- Premarin Vaginal Cream®
- Replens Long-Lasting Vaginal Moisturizer®

V. Summary

The treatment of dryness of mouth, as well as nasal and vaginal symptoms, is important for the symptomatic relief of the SS. However, in the “real” world of rheumatology where time per patient is limited and more “life threatening issues” must be assessed—a good approach is to refer the patient to printed material or to relevant websites. In our clinic, we use e-mail to send copies of information

(such as the Tables in this paper) to the patient. This allows the patient to concentrate on the overview of treatment at their leisure and formulate their questions for the next revisit.

The composition of tears and saliva are both quite complex, so much more is involved than simply replacement of “water.” Indeed, mucins and lipids may govern the stability of tear film and its evaporative rate. This is the reason that patients’ complaints of dry eyes or mouth correlate poorly with tear flow (Schirmer’s test) or saliva flow. The patient is telling us that the problem is the increased “friction” or “viscosity” as they move the lid over the orbit or the tongue around the mouth.

Treatment depends on a combination of measures to preserve existing tears/saliva, replacement of the tear/saliva, and new methods to create improve lubricating vehicles. The section on systemic therapies will concentrate on methods to decrease the inflammatory response that serves as the cause of the glandular dysfunction.

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